

Appl. No.: 09/973,375

Filed: 10/09/01

Page 2

REMARKS

Status of the Claims

Claims 1-20 have been rejected. Claims 1-20 remain pending.

The Rejection of the Claims Under 35 U.S.C. §103 Should Be Withdrawn

Claims 1-20 were rejected under 35 U.S.C. §103 as being obvious in view of Gee *et al.* (RE 35,517), Roof *et al.* (1994) *Experimental Neurology* 129:64-69; Roof *et al.* (1992) *Restorative Neurology and Neuroscience* 4:425-427; and Roof *et al.* (1997) *Molecular and Chemical Neuropathology* 31:1-11 and further in view of U.S. Patent No. 5,068,226. This rejection is respectfully traversed.

Roof *et al.* (1992) teach the administration of progesterone to rats following a frontal contusion reduces brain edema. Roof *et al.* (1994) teach the administration of progesterone to rats following a frontal contusion reduces brain edema, improves rat performance in the Morris water maze spatial navigation task, and decreases neuronal degeneration in the medial dorsal thalamic nucleus. Roof *et al.* (1997) administered progesterone to rats following a frontal contusion and found that approximately one-third of 8-isoPGF_{2α} found in control rats. Roof *et al.* (1997) asserts that this data supports that progesterone has antioxidant effects. None of these references by Roof *et al.* teach or suggest the administration of allopregnanolone to treat a traumatic CNS injury or reduce neurodegeneration following a traumatic CNS injury.

Gee *et al.* (RE. 35,517) performs *in vitro* binding studies and demonstrates that certain progesterone metabolites, including allopregnanolone, interact with the GABA/GBR complex at sites that are distinct from the site of interaction of barbiturates and other characterized modulators of GABA/GBR activity. See, Table 2 and Figures 1-3. Gee *et al.* also perform *in vivo* studies in which mice were administered a progesterone metabolite and 10 minutes later TBPS was injected into the mouse, resulting in TBPS-induced convulsions. The time to onset of myoclonus (presence of forelimb clonic activity) was assayed (see, column 15 and 16). Figure 4 demonstrates that certain progesterone metabolites, including allopregnanolone, delayed the onset of myoclonus.

Appl. No.: 09/973,375

Filed: 10/09/01

Page 3

U.S. Patent No. 5,068,226 teaches the administration of cyclodextrins to facilitate iontophoretic administration of active agents to patients. U.S. Patent No. 5,068,226 does not teach or suggest that any progesterone derivative could be successfully used to treat a traumatic CNS injury.

While the Examiner acknowledges that the prior art does not expressly disclose the employment of allopregnanolone in a method for treating a central nervous system injury or for decreasing neurodegeneration in a subject following a traumatic CNS injury (page 3, paragraph 2 of Office Action mailed July 1, 2003), the Examiner concludes that the cited references render the claims of the invention obvious. Applicants continue to maintain that a *prima facie* case of obviousness has not been established.

I. First, a *prima facie* case of obviousness requires a motivation to combine the references. "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 16 USPQ 2d 1430 (Fed. Cir. 1990). The cited art fails to satisfy this requirement.

The Examiner asserts in the July 1, 2003 Office Action (page 4) that Roof *et al.* (1997) teaches "progesterone's neuroprotective effects are through its interaction with GABA..." (emphasis in original) and further states on page 5, paragraph 2, that Roof *et al.* teaches progesterone and its metabolites, such as allopregnanolone, are known to share the same mechanism of action on their neuroprotective effects. Applicants do not agree with these conclusions. The Examiner's attention is drawn to the accompanying declaration filed under 37 C.F.R. §132 that addresses these assertions. Specifically sections 4b and 4c of the declaration discusses the inaccuracies of Examiner's comments and clearly demonstrates that the neuroprotective effects of progesterone remain unknown and could act via several biological mechanisms.

In providing motivation to combine Roof *et al.* and Gee *et al.*, the Examiner continues to equate the neuroprotective effects of progesterone following a traumatic CNS injury with modulating GABA. As previously made of record, this conclusion is inaccurate. Applicants note that the Examiner has failed to provide evidences for this assertion as required by MPEP

Appl. No.: 09/973,375

Filed: 10/09/01

Page 4

2144.02 and 2144.03. However, to expedite prosecution, this issue has been addressed in the accompanying 132 declaration. Specifically, the Examiner's attention is drawn to sections 4b and 4f of the declaration that demonstrates that modulating GABA is not equivalent to treating a traumatic brain injury.

Applicants again clarify that a traumatic injury to the CNS is *not* the disruption of the GABA system, but rather, as indicated on page 2, lines 28 and page 3, lines 3 of the specification, a traumatic injury to the central nervous system leads to *a cascade of physiological events that lead to neuronal loss*.

Following a traumatic injury to the central nervous system, *a cascade of physiological events* leads to neuronal loss including, for example, an inflammatory immune response and excitotoxicity resulting from the initial impact disrupting the glutamate, acetylcholine, cholinergic, GABA_A, and NMDA receptor systems. In addition, the traumatic CNS injury is frequently followed by brain and/or spinal cord edema that enhances the cascade of injury and leads to further secondary cell death and increased patient mortality. (emphasis added)

This point is again expressed in the specification on page 5, lines 8-15 that clearly states "a traumatic injury to the CNS results in *multiple physiological events* that impact the extent and rate of neurodegeneration and thus the final outcome of the injury." Accordingly, in view of the statements above and the accompanying 132 declaration, the teachings of Roof et al. (1997) have been mischaracterized.

The prior art itself must provide the skilled artisan the motivation to make the claimed invention. As traumatic injury to the central nervous system leads to *a cascade of physiological events that lead to neuronal loss*, one of skill in the art would not equate modulating activity of the GABA receptor with successful treatment of a traumatic injury to the CNS. Accordingly, one of skill would not be motivated to combine the teachings of Gee et al. and Roof et al. Applicants continue to maintain the claims of the present invention are being used as a guide to select references at random that mention various aspects of the claimed invention. None of the cited references would guide one of skill in the art to select allopregnanolone, *among the multitude of progesterone metabolites*, and administer this compound to a subject having a

Appl. No.: 09/973,375

Filed: 10/09/01

Page 5

traumatic CNS injury. As there is no basis in the art for combining or modifying the cited references, a *prima facie* case of obviousness has not been established.

II. A *prima facie* case of obviousness further requires the cited prior art to provide a reasonable expectation of success. Applicants maintain that the cited art fails to provide a reasonable expectation that the administration of allopregnanolone to a subject would successfully treat a *traumatic CNS injury* or decrease neurodegeneration following a *traumatic CNS injury* as claimed by the instant invention. First, the guidance provided by the cited art must be sufficiently specific to direct the attention of one skilled in the art to the selection of parameters and choices necessary to obtain the claimed invention. None of the references cited demonstrate or suggest the administration of allopregnanolone to treats a *traumatic CNS injury* or decrease neurodegeneration following a *traumatic CNS injury* as claimed by the instant invention. The art therefore fails to inherently or explicitly suggest the administration of allopregnanolone to a subject having a *traumatic* (i.e., physical force) CNS injury.

Moreover, the initial impact of a traumatic injury to the CNS produces many physiological events, including the disruption of multiple receptors/neurotransmitters. Therefore, modulating the activity of a single receptor as taught by Gee *et al.* is hardly sufficient to provide a reasonable expectation that allopregnanolone would successfully treat the traumatic CNS injury as claimed by the instant invention. See, sections 4c and 4f of the accompanying 132 declaration. Consequently, the prior art offers no suggestion or expressed expectation that administration of allopregnanolone would successfully treat a traumatic brain injury.

The Examiner continues to assert that allopregnanolone and progesterone have the "the same therapeutic usefulness" (page 6, lines 3 of the July 1, 2003 Office Action) and that, "progesterone and its metabolites such as allopregnanolone are known to share the same mechanism of action on their neuroprotective effects through their interaction with GABA." These conclusions are not supported by the cited art. Again, the Examiner has failed to satisfy the requirements of MPEP 2144.02 and 2144.03 and provide evidence for those conclusions. To expedite prosecution, Applicants respond to these assertions in the accompanying 132 declaration. Specifically, the Examiner's attention is drawn to sections 4b, 4c, 4d, and 4e of the

Appl. No.: 09/973,375

Filed: 10/09/01

Page 6

132 declaration that outlines that the mechanism of action by which progesterone and allopregnanolone mediate their neuroprotective effects is unknown and further concludes that one of skill would not assume progesterone and allopregnanolone have identical mechanisms of action.

The Examiner continues to assert that "allopregnanolone is also known to possess higher potency and efficacy than progesterone" based on the teachings of Gee *et al.* (page 5, lines 14-16 of the Office Action mailed July 1, 2003). Applicants disagree with this assertion. As outlined in section 4a of the 132 declaration, Gee *et al.* teach that both progesterone and many of its metabolites bind with high affinity to a unique GABA/GBR complex and that these metabolites delay onset of myoclonus following TBPS induced seizures in mice. There is no data demonstrating that progesterone and allopregnanolone are effective at treating other disease states, such as traumatic brain injury, and certainly no teaching that *all* of progesterone's beneficial effects are related to progesterone's conversion into its various metabolites.

Moreover, the Examiner states that Roof *et al.* (1997) teaches that "progesterone's neuroprotective effects are through its interaction with GABA, and progesterone and some of its metabolites are known to bind to and potentiate activity of GABAa receptor" (page 4, Office Action mailed July 1, 2003). As Applicants have outlined in detail above, and also address in sections 4b of the accompanying 132 declaration, Roof *et al.* provides no such teachings. Roof *et al.* (1997) speculate that progesterone could act via "radical scavenging and membrane stabilization" (page 7, paragraph 2), could interact with GABAa receptor, and/or antagonize the glutamate receptor system (page 7, paragraph 3). Roof *et al.* all never concludes progesterone's neuroprotective activity results from *only* GABA receptor modulation. Again, a traumatic central nervous system injury does not simply disrupt the GABA receptor system. A traumatic injury to the central nervous system leads to *a cascade of physiological events that lead to neuronal loss*. This point is again expressed in the specification on page 5, lines 8-15 that clearly states that "a traumatic injury to the CNS results in *multiple physiological events* that impact the extent and rate of neurodegeneration and thus the final outcome of the injury". Modulation of only the GABA receptor provides no assurances that one could treat a traumatic central nervous

Appl. No.: 09/973,375

Filed: 10/09/01

Page 7

system injury as asserted in the office action. Accordingly, the Examiner has failed to provide sufficient evidence that the cited prior art provides a reasonable expectation of success.

As previously made of Record, pages 20-32 of the instant specification demonstrates for the first time that following a traumatic central nervous system injury, the administration of allopregnanolone significantly reduces cerebral edema when compared to control rats (see Figure 1); significantly increases the learning rate compared to control rats (See Figure 2); and, significantly delays the synthesis and level of activity of inflammatory cytokines (Figures 3 and 4). The Examiner, however, states that the results set forth in the specification of the instant invention are "clearly expected and not unexpected based on the cited prior art" and therefore concludes that a reasonable expectation of success exists. The Examiner is reminded that one cannot base obviousness upon what a person skilled in the art might try or might find obvious to try but rather must consider what the prior art would have led a person skilled in the art to do. As discussed above, Gee *et al.* teaches that progesterone and its metabolites have varying activity and offer no teaching that allopregnanolone could treat a *traumatic* injury to the CNS. Similarly, Roof *et al.* only teach the administration of allopregnanolone following a frontal contusion. Prior to the present invention, one of skill in the art would not have recognized that allopregnanolone could be used to treat a traumatic CNS injury or decrease neurodegeneration as claimed by the present invention. Therefore, contrary to the Examiner's assertion, there was not a reasonable chance of success.

Moreover, on page 7 of the Office Action dated July 1, 2003 continues to maintain that since Examples 6 and 7 of the present application administer progesterone, the "Applicant clearly acknowledges that progesterone and its particular metabolite, allopregnanolone, have the same therapeutic usefulness." *Applicants never stated or suggested that progesterone and allopregnanolone had the same therapeutic usefulness.* The examples using progesterone simply provide further evidence of the activity of progesterone on behavior and lesion size and the use of a cyclodextrin vehicle in administration. These experiments do not indicate that the results should be extrapolated to allopregnanolone. Examples 6 and 7 do not represent examples of the invention presently being claimed, and the Examiner is respectfully requested to withdraw

Appl. No.: 09/973,375

Filed: 10/09/01

Page 8

her assertion regarding Applicant's admission. If this assertion is maintained, the Examiner is respectfully requested to cite the authority for this conclusion.

III. In Summary, in view of the comments above and the statements appearing in the accompanying 132 declaration, Applicants maintain that the art cited by the Examiner does not provide the motivation to combine the reference nor do the references provide a reasonable expectation of success. The law is clear that without motivation to combine the references and a reasonable expectation of success, a rejection under 35 USC §103 fails. In summary, Applicants maintain a *prima facie* case of obviousness has not been established. Applicants respectfully submit that the claimed methods are not obvious in view of the cited references and respectfully request that the rejection of claims 1-20 under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully submit that the rejection of claims 1-20 under 35 U.S.C. §103 is overcome. Accordingly, Applicants submit that this application is in condition for allowance. Early notice to this effect is solicited.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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Appl. No.: 09/973,375

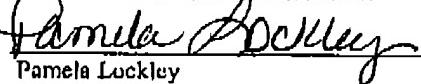
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Page 9

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FROM: Kelly J. Williamson
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In re: Stein *et al.* Confirmation No.: 5877
Application No.: 09/973,375 Group No.: 1617
Filed: 10/09/01 Examiner: S. Jiang
For: METHODS FOR THE TREATMENT OF A TRAUMATIC CENTRAL
NERVOUS SYSTEM INJURY

Attachments

Request for three month extension(1 page)
Amendment(9 pages)
132 Declaration(7 pages)

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